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 NEWS  3  Feb 06  Engineering Information Encompass files have new names
 NEWS  4  Feb 16  TOXLINE no longer being updated
 NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07  DGENE Reload

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               CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP),
               AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2001
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=> file embase medline biosis caplus uspatfull

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CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

=> s candesartan

L1        2032 CANDESARTAN

=> s lesartan

L2           2 LESARTAN

=> s valsartan

L3        1462 VALSARTAN

=> s ibesartan

L4           1 IBESARTAN

=> s l1 and l3

L5         356 L1 AND L3

=> s l5 and l2 and l4

L6           0 L5 AND L2 AND L4

=> s l5 and l2

L7           0 L5 AND L2

=> s l5 and tasosartan

L8          62 L5 AND TASOSARTAN

=> s l8 and telmisartan

L9          52 L8 AND TELMISARTAN

=> s l9 and eprosartan

L10         50 L9 AND EPROSARTAN

=> s l10 and ACE inhibitor

L11         19 L10 AND ACE INHIBITOR

=> dup rem

ENTER L# LIST OR (END):l11

PROCESSING COMPLETED FOR L11
L12          15 DUP REM L11 (4 DUPLICATES REMOVED)

=> s l12 and py<1998

   2 FILES SEARCHED...
   3 FILES SEARCHED...
L13          2 L12 AND PY<1998

=> d l13


L13  ANSWER 1 OF 2  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN   97328208  EMBASE
DN   1997328208
TI   Hypertension update: Low dose drug combination for the treatment of
```

hypertension.
AU Chrysanthakopoulos S.G.
CS S.G. Chrysanthakopoulos, 5850 W. Wilshire Blvd, Oklahoma City, OK 73132-4904, United States
SO Hellenic Journal of Cardiology, (1997) 38/2 (73-83).
Refs: 78
ISSN: 1011-7970 CODEN: HLKEAE
CY Greece
DT Journal; General Review
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English; Greek

=> d l13 2

L13 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97160226 EMBASE
DN 1997160226
TI Angiotensin II receptor antagonists - antihypertensive agents.
AU Burnier M.; Brunner H.R.
CS M. Burnier, Div. of Hypertension/Vascular Med., 1011 Lausanne, Switzerland
SO Expert Opinion on Investigational Drugs, (1997) 6/5 (489-500).
Refs: 66
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LA English
SL English

=> d l13 1-2 ab

L13 ANSWER 1 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB Fixed-dose combination treatment of hypertension provides simplicity of treatment regimen, increased compliance by the patient and improved cost of therapy. On the other hand, impairs selective titration of component drugs and the choice of a third drug if necessary. However, the development of new, more physiologic, antihypertensive drugs, allows fixed-dose drug combination to be used in the majority of cases with good blood pressure control. In addition, fixed-dose drug combination provides for combination of low doses of the component drugs which decreases or reverses each others side effects without compromising blood pressure control and at the same time improving quality of life. The most commonly used fixed-dose drug combinations include: (1) Diuretics with potassium sparing agents. (2) Beta blockers with diuretics. (3) Angiotensin converting enzyme (**ACE**) **inhibitors** with diuretics. (4) Angiotensin II antagonists with diuretics. (5) **ACE** **inhibitors** with calcium channel blockers.

L13 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB Blockade of the renin-angiotensin system (RAS) is now recognised as an effective approach for the treatment of hypertension and congestive heart failure (CHF). Today, it is possible to antagonise the effects of angiotensin II more specifically by blocking its receptors using non-peptide receptor antagonists. These compounds, which at first were used to identify the various subtypes of angiotensin II receptors, are now

available clinically. Some of them have recently been launched on the market and several others are preregistered for the treatment of hypertension. These new molecules are as effective as angiotensin converting enzyme (**ACE**) **inhibitors** at lowering blood pressure in hypertensive patients, and appear to have similar systemic and
renal haemodynamic properties in patients with CHF and renal diseases. Large- scale clinical trials such as the LIFE, the ELITE and the RENAAL studies are now underway to investigate the long-term benefits of one of these agents in hypertension, heart failure and Type II diabetic nephropathy. The major clinical advantage of AT1 receptor antagonists is that, in contrast to **ACE inhibitors**, they do not induce cough. With the more widespread use of AT1 receptor antagonists, two unresolved questions remains unanswered: what is the role of AT2 receptors? Are the unblocked effects of angiotensin II on AT1 receptor sites of any clinical relevance to the safety profile or efficacy of AT1 receptor antagonists? Another interesting question is whether the combination of an **ACE inhibitor** with an AT1 receptor antagonist is advantageous. Studies attempting to answer these questions are underway and will certainly enable researchers to define more precisely the role and the advantages of these new specific non-peptide AT1 receptor antagonists in the treatment of hypertension and heart failure.

=> d kwic 1-2

L13 ANSWER 1 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
SO Hellenic Journal of Cardiology, (1997) 38/2 (73-83).
Refs: 78
ISSN: 1011-7970 CODEN: HLKEAE
AB . . . used fixed-dose drug combinations include: (1) Diuretics with potassium sparing agents. (2) Beta blockers with diuretics. (3) Angiotensin converting enzyme (**ACE**) **inhibitors** with diuretics. (4) Angiotensin II antagonists with diuretics. (5) **ACE inhibitors** with calcium channel blockers.
CT Medical Descriptors:
*combination . . .
PD, pharmacology
bendroflumethiazide plus nadolol: DO, drug dose
bendroflumethiazide plus nadolol: DT, drug therapy
bendroflumethiazide plus nadolol: PD, pharmacology
bendroflumethiazide plus nadolol: CB, drug combination
candesartan hexetil: DT, drug therapy
candesartan hexetil: CB, drug combination
candesartan hexetil: DO, drug dose
captopril plus hydrochlorothiazide: CB, drug combination
captopril plus hydrochlorothiazide: DT, drug therapy
captopril plus hydrochlorothiazide: PD, pharmacology
captopril plus hydrochlorothiazide:. . . drug dose
enalapril plus hydrochlorothiazide: PD, pharmacology
enalapril plus hydrochlorothiazide: DT, drug therapy
enalapril plus hydrochlorothiazide: DO, drug dose
enalapril plus hydrochlorothiazide: CB, drug combination
eprosartan: DO, drug dose
eprosartan: CB, drug combination
eprosartan: DT, drug therapy
hydrochlorothiazide plus triamterene: DT, drug therapy
hydrochlorothiazide plus triamterene: PD, pharmacology
hydrochlorothiazide plus triamterene: CB, drug combination
hydrochlorothiazide plus triamterene: DO,. . . PD, pharmacology
metoprolol tartrate: DT, drug therapy
metoprolol tartrate: CB, drug combination
prinzide: DT, drug therapy
prinzide: DO, drug dose

prinzide: PD, pharmacology
prinzide: CB, drug combination
tasosartan: CB, drug combination
tasosartan: DO, drug dose
tasosartan: DT, drug therapy
telmisartan: DT, drug therapy
telmisartan: DO, drug dose
telmisartan: CB, drug combination
triamterene: DT, drug therapy
triamterene: PD, pharmacology
triamterene: CB, drug combination
triamterene: DO, drug dose
valsartan: CB, drug combination
valsartan: DO, drug dose
valsartan: DT, drug therapy

RN. . . ethyl 4 [2' (1h tetrazol 5 yl)biphenyl 4 ylmethoxy]quinoline) 135015-84-8; (aldactazine) 76270-06-9; (amiloride plus hydrochlorothiazide) 57017-78-4; (atenolol plus chlortalidone) 73677-19-7;
(**candesartan** hexetil) 145040-37-5; (**eprosartan**) 133040-01-4; (hydrochlorothiazide plus triamterene) 14124-50-6; (irbesartan) 138402-11-6; (losartan potassium) 124750-99-8; (metoprolol tartrate) 56392-17-7; (**tasosartan**) 145733-36-4; (**telmisartan**) 144701-48-4; (triamterene) 396-01-0; (**valsartan**) 137862-53-4

L13 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

SO Expert Opinion on Investigational Drugs, (1997) 6/5 (489-500).
Refs: 66
ISSN: 1354-3784 CODEN: EOIDER

AB . . . and several others are preregistered for the treatment of hypertension. These new molecules are as effective as angiotensin converting enzyme (**ACE**) **inhibitors** at lowering blood pressure in hypertensive patients, and appear to have similar systemic and
renal haemodynamic properties in patients with. . . heart failure and Type II diabetic nephropathy. The major clinical advantage of AT1 receptor
antagonists is that, in contrast to **ACE inhibitors**, they do not induce cough. With the more widespread use of AT1 receptor antagonists, two unresolved questions remains unanswered: what. . . relevance to the safety profile or efficacy of AT1 receptor antagonists? Another interesting question is whether the combination of an **ACE inhibitor** with an AT1 receptor antagonist is advantageous. Studies attempting to answer these questions are underway and will certainly enable researchers. . .

CT Medical Descriptors:
*hypertension: . . .
(1h tetrazol 5 yl) 4 biphenylyl]methoxy]pyridine: CT, clinical trial
antihypertensive agent: CT, clinical trial
antihypertensive agent: DT, drug therapy
antihypertensive agent: CB, drug combination
candesartan hexetil
blopres
candesartan: CT, clinical trial
candesartan: DT, drug therapy
eprosartan: CT, clinical trial
eprosartan: DT, drug therapy
hydrochlorothiazide plus losartan
imidazopyridine derivative: DT, drug therapy
imidazopyridine derivative: CT, clinical trial
irbesartan: CT, clinical trial
irbesartan: DT, drug therapy
losartan: DT,. . . therapy
peptide derivative: CT, clinical trial
piperazine derivative: DT, drug therapy

piperazine derivative: CT, clinical trial
quinazolinone derivative: CT, clinical trial
quinazolinone derivative: DT, drug therapy
tasosartan: DT, drug therapy
tasosartan: CT, clinical trial
telmisartan: DT, drug therapy
telmisartan: CT, clinical trial
tetrahydroisoquinoline derivative: CT, clinical trial
tetrahydroisoquinoline derivative: DT, drug therapy
unindexed drug
valsartan: DT, drug therapy
valsartan: CT, clinical trial
unclassified drug

RN. . . yl) 4 biphenylyl]methyl] 3h imidazo[4,5 b]pyridine) 136042-19-8; (3 methoxy 2,6 dimethyl 4 [[2' (1h tetrazol 5 yl) 4 biphenylyl]methoxy]pyridine) 139958-16-0; (**candesartan** hexetil) 145040-37-5; (**candesartan**) 139481-59-7; (**eprosartan**) 133040-01-4; (irbesartan) 138402-11-6; (losartan) 114798-26-4; (losartan potassium) 124750-99-8; (n [[4' [(2 ethyl 5,7 dimethyl 3h imidazo[4,5 b]pyridin 3 yl)methyl] 2 biphenylyl]sulfonyl]benzamide) 157263-00-8; (**tasosartan**) 145733-36-4; (**telmisartan**) 144701-48-4; (**valsartan**) 137862-53-4

=> d hist

(FILE 'HOME' ENTERED AT 12:24:01 ON 08 JUN 2001)

FILE 'EMBASE, MEDLINE, BIOSIS, CAPLUS, USPATFULL' ENTERED AT 12:24:22 ON 08 JUN 2001

L1	2032	S	CANDESARTAN
L2	2	S	LESARTAN
L3	1462	S	VALSARTAN
L4	1	S	IBESARTAN
L5	356	S	L1 AND L3
L6	0	S	L5 AND L2 AND L4
L7	0	S	L5 AND L2
L8	62	S	L5 AND TASOSARTAN
L9	52	S	L8 AND TELMISARTAN
L10	50	S	L9 AND EPROSARTAN
L11	19	S	L10 AND ACE INHIBITOR
L12	15	DUP REM	L11 (4 DUPLICATES REMOVED)
L13	2	S	L12 AND PY<1998

L6 ANSWER 12 OF 41 USPATFULL
TI Treatment of **congestive heart failure**
PI US 5610134 19970311 <--
AB Methods of enhancing myocardial contractility and cardiac performance in a mammal with **congestive heart failure** are disclosed. In a first method a mammal with **congestive heart failure** is treated by administering to the mammal an effective amount of a combination of growth hormone (GH) and insulin-like growth. . . comprises administering to the mammal an effective amount of a combination of GH and IGF-I in the presence of an **ACE inhibitor**. This method results in enhancement of myocardial contractility and cardiac performance above the level achieved with ACE inhibition alone. Preferably. . .
SUMM This invention relates to the field of treating patients having **congestive heart failure** with growth hormone and insulin-like growth factor I in the presence or absence of an angiotensin-converting enzyme (**ACE**) **inhibitor**.
SUMM . . . for two weeks improved cardiac function by increasing ventricular contractility and by decreasing peripheral vascular resistance in conscious rats with **congestive heart failure**. Yang, R. et al., Clinical Research 42(2):325A (1994).
SUMM . . . U. et al., Basic Res. Cardiol. 83:647-654 (1988). Acute intravenous administration (infusion or bolus injection) of IGF-I produces increases in **stroke** volume and cardiac output in normal lambs. Gluckman et al., PCT WO 92/11865 (1992). In rats with doxorubicin induced cardiomyopathy, chronic treatment with IGF-I for 3 weeks increases cardiac output and **stroke** volume. Ambler, G. R. et al., Cardiovascular Research 27:1368-1373 (1993).
SUMM Heart failure affects approximately three million Americans. New cases of heart failure number about 400,000 each year. **Congestive heart failure** is a syndrome characterized by left ventricular dysfunction, reduced exercise tolerance, impaired quality of life, and markedly shortened life expectancy.. . . cardiac output with consequent systemic arterial and venous vasoconstriction. This vasoconstriction, which promotes the vicious cycle of further reductions of **stroke** volume followed by an increased elevation of vascular resistance, appears to be mediated, in part, by the renin-angiotensis system. The. . . Cohn, J. N. et al., N. England J. Med. 325(5):303-310 (1991); Captopril Multicenter Research Group, J.A.C.C. 2(4):755-763 (1983). Angiotensin-converting enzyme (**ACE**) **inhibitors**, such as captopril, have become standard therapy for patients with **congestive heart failure**. These drugs improve hemodynamic profile and exercise tolerance and reduce the incidence of morbidity and mortality in patients with **congestive heart failure**. Kramer, B. L. et al., Circulation 67(4):807-816 (1983); Captopril Multicenter Research Group, J.A.C.C. 2(4):755-763 (1983); The CONSENSUS Trial Study Group,. . . Engl. J. Med. 316(23):1429-1435 (1987); The SOLVD Investigators, N. Engl. J. Med. 325(5):293-302 (1991). However, despite proven efficacy, response to **ACE inhibitors** has been limited. Improvement of functional capacity and exercise time is only small and mortality, although reduced, continues to be. . .
SUMM Accordingly, it is an object of this invention to provide a method of treatment for patients with **congestive heart failure**, the method comprising administering to the patient GH and IGF-I in addition to an **ACE inhibitor**. It is well known, that captopril alone, for example, improves cardiac function

by decreasing peripheral vascular resistance. Captopril together with. . .

SUMM It is another object of this invention to provide a method of treatment for patients with **congestive heart failure**, the method comprising treating the patients with an effective amount of a combination of GH and IGF-I in the absence of an **ACE inhibitor**. The administration of GH and IGF-I in combination produces improvement of cardiac performance by increased ventricular contractility and decreased peripheral. . .

SUMM Improvement in cardiac performance for patients with **congestive heart failure** may be achieved in patients being treated with **ACE inhibitors** by adding to the treatment regimen a combination of GH and IGF-I. Improvement in cardiac performance in these patients may also be achieved by administration of GH/IGF-I and an **ACE inhibitor** from the outset of treatment.

SUMM The present invention achieves these objects by providing a method of treatment of **congestive heart failure**, the method characterized by administration of an effective amount of GH and IGF-I (GH/IGF-I) with or without an **ACE inhibitor**.

SUMM In one aspect, the present invention provides a method of treating a mammal exhibiting **congestive heart failure** comprising administering to the mammal an effective amount of a combination of GH and IGF-I and an **ACE inhibitor**. Administration of GH and IGF-I may be started after a period of treatment with the **ACE inhibitor**.

SUMM In another aspect, the invention provides a method of treating a mammal exhibiting **congestive heart failure** comprising administering to said mammal an effective amount of a combination of GH and IGF-I in the absence of an **ACE inhibitor**.

DRWD FIG. 6b shows the effect of GH/IGF-I (hatched bars) and vehicle alone (open bars) on **stroke** volume index (SVI) in water-treated and captopril-treated rats. * P<0.05, ** P<0.01, compared to the respective vehicle group. ##P<0.01, compared. . .

DETD As used herein, "SV" refers to **stroke** volume. The **stroke** volume is measurable as CO/HR.

DETD As used herein, "SVI" refers to **stroke** volume index. The **stroke** volume index is measurable as SV/BW.

DETD As used herein "**congestive heart failure**" refers to a syndrome characterized by left ventricular dysfunction, reduced exercise tolerance, impaired quality of life, and markedly shortened life. . . vasoconstriction, which appears to be mediated, in part, by the renin-angiotensis system, promotes the vicious cycle of further reductions of **stroke** volume followed by an increased elevation of vascular resistance.

DETD As used herein "treatment" refers to induction of increased myocardial contractility and cardiac performance in patients experiencing **congestive heart failure**, as well as to prevention of **congestive heart failure**. Where the combination of GH and IGF-I is used in conjunction with an **ACE inhibitor**, the level of increased myocardial contractility and cardiac performance is increased above that resulting from use of the **ACE inhibitor** alone.

DETD As used herein, "**ACE inhibitor**" refers to angiotensin-converting enzyme inhibiting drugs which prevent the conversion of angiotensin I to angiotensin II. The **ACE inhibitors** may be beneficial in **congestive heart failure** by reducing systemic vascular resistance and relieving circulatory congestion. The **ACE inhibitors** include but are not limited to those designated by the trademarks Accupril.RTM. (quinapril), Altace.RTM. (ramipril), Capoten.RTM. (captopril), Lotensin.RTM. (benazepril), Monopril.RTM. (fosinopril), Prinivil.RTM. (lisinopril), Vasotec.RTM. (enalapril), and Zestril.RTM. (lisinopril). One example of an **ACE inhibitor** is that sold under the trademark Capoten.RTM..

Generically referred to as captopril, this **ACE inhibitor** is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline.

DETD In the treatment of **congestive heart failure** by GH and IGF-I in combination, the GH and IGF-I compositions will be formulated, dosed, and administered in a fashion. . . thus determined by such considerations and are amounts that improve cardiac performance or ameliorate other conditions of similar importance in **congestive heart failure** patients.

DETD The effective amount of **ACE inhibitor** to be administered, if employed, will be at the physician's or veterinarian's discretion. Dosage administration and adjustment is done to achieve optimal management of **congestive heart failure** and ideally takes into account use of diuretics or digitalis, and conditions such as hypotension and renal impairment. The dose. . . and the specific patient being treated. Typically the amount employed will be the same dose as that used if the **ACE inhibitor** were to be administered without GH and IGF-I.

DETD . . . administration in tablet or capsule form. A discussion of the dosage, administration, indications and contraindications associated with captopril and other **ACE inhibitors** can be found in the Physicians Desk Reference, Medical Economics Data Production Co., Montvale, N.J. 2314-2320 (1994).

DETD Use of GH/IGF-I to treat **Congestive Heart Failure** With and Without

DETD The goal of this study was to evaluate the cardiac effects of human GH/IGF-I in rats with **congestive heart failure** with and without prior and concurrent treatment with either captopril or water

DETD . . . Animal Use" adopted Nov. 11, 1984 by the American Heart Association. After 4-6 weeks of ligation, myocardial infarction resulted in **congestive heart failure** in rats.

DETD . . . VR-16 simultrace recorders (Honeywell Co., N.Y.) and cardiac output (CO) was digitally obtained by the microcomputer. From the CO the **stroke** volume (SV), cardiac index (CI), **stroke** volume index (SVI), and systemic vascular resistance (SVR) can be calculated.

DETD Treatment for **congestive heart failure** with a combination of GH and IGF-I resulted in a significant increase in left ventricular maximum dP/dt, both in the. . .

DETD . . . decreases in arterial pressure, left ventricular end-diastolic pressure and peripheral vascular resistance. These changes resulted in increased cardiac output and **stroke** volume in the test animals. These are the well known benefits of ACE inhibition which are manifest in humans and. . .

DETD GH and IGF-I added to the treatment regimen of a mammal with **congestive heart failure** after an initial period of treatment with captopril induced effects of increased myocardial contractility and cardiac performance which were apparent. . with captopril, GH, and IGF-I. The data suggest that captopril in combination with GH and IGF-I improves cardiac performance in **congestive heart failure.**

DETD These results suggest that after a period of treatment with captopril or other **ACE inhibitor**, a patient with **congestive heart failure** will benefit from addition of GH and IGF-I to the treatment regimen. These results also suggest that a patient will benefit from a combination of GH and IGF-I, even in the absence of an **ACE inhibitor.** Patients benefitting from a combination of GH and IGF-I in the absence of an **ACE inhibitor** are those for whom an **ACE**

inhibitor is contraindicated and those who cannot tolerate the side effects of an **ACE inhibitor**.

DETD Proposed Clinical Treatment of **Congestive Heart Failure**

DETD **Diabetes** mellitus or impaired glucose tolerance.

CLM What is claimed is:

1. A method of treating **congestive heart failure** in a mammal, said method comprising administering to said mammal an effective amount of a combination of GH, IGF-1, and an **ACE inhibitor**.

. . . The method of claim 1 wherein administration of GH and IGF-I is begun following a period of treatment with the **ACE inhibitor** alone.

3. The method of claim 1 wherein the GH, IGF-I, and **ACE inhibitor** are administered together from the outset of treatment.

4. The method of claim 1 wherein the **ACE inhibitor** is captopril.

9. The method of claim 1 wherein the **congestive heart failure** results from acute or chronic ischemia.

10. The method of claim 1 wherein the **congestive heart failure** results from myocardial infarction.

AN 97:20504 USPATFULL|

TI Treatment of **congestive heart failure**|

IN Clark, Ross G., Pacifica, CA, United States
Jin, Hongkui, San Bruno, CA, United States
Paoni, Nicholas F., Belmont, CA, United States
Yang, Renhui, San Bruno, CA, United States

PA Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)

PI US 5610134 19970311 <--

AI US 1994-333909 19941103 (8)

RLI Continuation of Ser. No. US 1994-284859, filed on 2 Aug 1994 which is a continuation of Ser. No. US 1994-227923, filed on 15 Apr 1994, now abandoned

DT Utility|

EXNAM Primary Examiner: Jordan, Kimberly|

LREP Hasak, Janet E.; Dreger, Walter H.|

CLMN Number of Claims: 10|

ECL Exemplary Claim: 1|

DRWN 13 Drawing Figure(s); 6 Drawing Page(s)|

LN.CNT 1257|

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 13 OF 41 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
TI **Angiotensin-converting enzyme inhibitors**, angiotensin II receptor antagonists and calcium channel blocking agents: A review of potential benefits and possible adverse reactions.
SO Journal of the American College of Cardiology, (1997) 29/7 (1414-1421). Refs: 46
ISSN: 0735-1097 CODEN: JACCDI
AB A review of recent studies suggests that the use of angiotensin-converting enzyme (**ACE**) **inhibitors** may be preferred (usually along with a diuretic drug) as initial therapy in several subsets of hypertensive patients (i.e., those with **diabetes** and nephropathy or with diminished left ventricular function with or without symptoms of heart failure). Limited long-term data are available. . . reduce reinfarction in patients with ischemic heart disease (however, mortality is nut reduced). Long-acting formulas of CCBs appear to decrease **congestive heart failure** in patients with dilated, but not ischemic, cardiomyopathy and to decrease **strokes** and arrhythmias in hypertensive subjects. Short-acting agents (primarily those that increase heart rate) may increase coronary heart disease events in. . .
CT Medical Descriptors:
*atherosclerosis: . . . therapy
*ischemic heart disease: DT, drug therapy
*ischemic heart disease: DI, diagnosis
clinical feature
congestive cardiomyopathy
disease association
heart arrhythmia
heart failure
heart left ventricle function
human
kidney disease
medical research
morbidity
mortality
priority journal
review
stroke
*angiotensin receptor antagonist: CB, drug combination
*angiotensin receptor antagonist: DT, drug therapy
*calcium channel blocking agent: CB, drug combination
*calcium channel blocking agent:. . .
AN 97193456 EMBASE
DN 1997193456
TI **Angiotensin-converting enzyme inhibitors**, angiotensin II receptor antagonists and calcium channel blocking agents: A review of potential benefits and possible adverse reactions.
AU Moser M.
CS Dr. M. Moser, 13 Murray Hill Road, Scarsdale, NY 10583, United States
SO Journal of the American College of Cardiology, (1997) 29/7 (1414-1421). Refs: 46
ISSN: 0735-1097 CODEN: JACCDI
PUI S 0735-1097(97)00096-X
CY United States
DT Journal; General Review

FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English

AN 97:76104 USPATFULL|
TI Treatment of **congestive heart failure**|
IN Clark, Ross G., Pacifica, CA, United States
Jin, Hongkui, San Bruno, CA, United States
Paoni, Nicholas F., Belmont, CA, United States
Yang, Renhui, San Bruno, CA, United States
PA Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)
PI US 5661122 19970826 <--
AI US 1994-284859 19940802 (8)
RLI Continuation of Ser. No. US 1994-227923, filed on 15 Apr 1994, now abandoned
DT Utility|
EXNAM Primary Examiner: Jordan, Kimberly|
LREP Hasak, Janet E.; Dreger, Walter H.|
CLMN Number of Claims: 8|
ECL Exemplary Claim: 1|
DRWN 13 Drawing Figure(s); 6 Drawing Page(s)|
LN.CNT 1425|
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of enhancing myocardial contractility and cardiac performance in
a mammal with **congestive heart failure** are disclosed. In a first method a mammal with **congestive heart failure** is treated by administering to the mammal an effective amount of a combination of growth hormone (GH) and insulin-like growth factor (IGF-I). A second method comprises administering to the mammal an effective amount of a combination of GH and IGF-I in the presence of an **ACE inhibitor**. This method results in enhancement of myocardial contractility and cardiac performance above the level achieved with ACE inhibition alone. Prefe

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SUMM Current therapy for heart failure is primarily directed to using angiotensin-converting enzyme (**ACE**) **inhibitors** and diuretics. While prolonging survival in the setting of heart failure, **ACE inhibitors** appear to slow the progression towards end-stage heart failure, and substantial numbers of patients on **ACE inhibitors** have functional class III heart failure. Moreover, **ACE inhibitors** consistently appear unable to relieve symptoms in more than 60% of heart failure patients and reduce mortality of heart failure. . .
SUMM . . . activation of physiological or compensatory hypertrophy can be beneficial in the setting of heart failure. In fact, the effects of **ACE inhibitors** have been purported not only to unload the heart, but also to inhibit the pathological hypertrophic response that has been. . .
SUMM Not only is there a need for an improvement in the therapy of heart failure such as **congestive heart failure**, but there is also a need to offer effective treatment for neurological disorders. Neurotrophic factors such as insulin-like growth factors,.
.
. means for enhancing neuronal survival, for example, as a treatment for neurodegenerative diseases such as amyotrophic lateral sclerosis, Alzheimer's disease, **stroke**, epilepsy, Huntington's disease, Parkinson's disease, and peripheral neuropathy. It would be desirable
to
provide an additional therapy for this purpose.
SUMM . . . object of the present invention to provide an improved therapy for the prevention and/or treatment of heart failure such as **congestive heart failure**, particularly the promotion of physiological forms of hypertrophy or inhibition of pathological forms of hypertrophy, and for the prevention and/or. . .
DETD . . . disorders include all neurodegenerative diseases, such as peripheral neuropathies (motor and sensory), amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, **stroke**, Huntington's disease, epilepsy, and ophthalmologic diseases such as those involving the retina, e.g., diabetic
retinopathy,
retinal dystrophy, and retinal degeneration. . .
DETD . . . the rate needed for the requirements of metabolizing tissues. Heart failure includes a wide range of disease states such as **congestive heart failure**, myocardial infarction, and tachyarrhythmia.
DETD As used herein, **"ACE inhibitor"** refers to angiotensin-converting enzyme inhibiting drugs which prevent the conversion of angiotensin I to angiotensin II. The **ACE inhibitors** may be beneficial in **congestive heart failure** by reducing systemic vascular resistance and relieving circulatory congestion. The **ACE inhibitors** include but are not limited to those designated by the trademarks Accupril.RTM. (quinapril), Altace.RTM. (ramipril), Capoten.RTM. (captopril), Lotensin.RTM. (benazepril) Monoopril.RTM. (fosinopril), Prinivil.RTM. (lisinopril), Vasotec.RTM. (enalapril), and Zestril.RTM. (lisinopril). One example of an **ACE inhibitor** is that sold under the trademark Capoten.RTM.. Generically referred to as captopril, this **ACE inhibitor** is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline.
DETD . . . administering a therapeutically effective amount of a CMF to the mammal. Optionally, the CHF is administered in combination with an

ACE inhibitor, such as captopril, in the case of **congestive heart failure**, or with another myocardiotrophic, anti-arrhythmic, or inotropic factor in the case of other types of heart failure or cardiac disorder,. . .

DETD For example, CHF may be useful in treating **congestive heart failure** in cases where **ACE inhibitors** cannot be employed or are not as effective. CHF optionally is combined with or administered in concert with other agents for treating **congestive heart failure**, including **ACE inhibitors**.

DETD The effective amount of **ACE inhibitor** to be administered, if employed, will be at the physician's or veterinarian's discretion. Dosage administration and adjustment is done to achieve optimal management of **congestive heart failure** and ideally takes into account use of diuretics or digitalis, and conditions such as hypotension and renal impairment. The dose. . . and the specific patient being treated. Typically the amount employed will be the same dose as that used if the **ACE inhibitor** were to be administered without CHF.

DETD . . . administration in tablet or capsule form. A discussion of the dosage, administration, indications and contraindications associated with captopril and other **ACE inhibitors** can be found in the Physicians Desk Reference, Medical Economics Data Production Co., Montvale, N.J. 2314-2320 (1994).

DETD . . . into the treatment of all neurodegenerative diseases by CHF, including peripheral neuropathies (motor and sensory), ALS, Alzheimer's disease, Parkinson's disease, **stroke**, Huntington's disease, and ophthalmologic diseases, for example, those involving the retina.

DETD . . . be one which increases ventricular contractility and decreases peripheral vascular resistance or ameliorates or treats conditions of similar importance in **congestive heart failure** patients. The progress of this therapy is easily monitored by conventional assays.

DETD . . . endothelin, neonatal rat myocardial cells in culture display several features of the in vivo cardiac muscle cell hypertrophy seen in **congestive heart failure**, including an increase in cell size and an increase in the assembly of an individual contractile protein into organized contractile. . .

DETD . . . heart beat, concentric or dilated hypertrophy, left ventricular systolic pressure, left ventricular mean pressure, left ventricular end-diastolic pressure, cardiac output, **stroke** index, histological parameters, ventricular size, wall thickness, etc.

DETD The purified CHF is also tested in a post-myocardial infarction rat model, which is predictive of human **congestive heart failure** in producing natriuretic peptide. Specifically, male Sprague-Dawley rats (Charles River Breeding Laboratories, Inc., eight weeks of age) are acclimated to. . .

DETD In clinical patients, myocardial infarction or coronary artery disease is the most common cause of heart failure. **Congestive heart failure** in this model reasonably mimics **congestive heart failure** in most human patients.

DETD . . . is monitored by VR-16 simultrace recorders (Honeywell Co., New York) and cardiac output (CO) is digitally obtained by the microcomputer. **Stroke** volume (SV)=CO/HR; Cardiac index (CI)=CO/BW; Systemic vascular resistance (SVR)=MAP/CI.

DETD . . . and ligated rat controls. This expected result would demonstrate that administration of CHF or CHF antagonist improves cardiac function in **congestive heart failure**. In sham rats, however, CHF or CHF antagonist administration at this dose is not expected to alter significantly cardiac function. . .

DETD . . . are determined at the time of re-evaluation, the dose would be adjusted upward. Concurrent medication doses (e.g., captopril as an

ACE inhibitor and diuretics) would be adjusted at the discretion of the study physician. After the maximum dose is administered for 8. . .

DETD . . . or peak exercise VO.sub.2 <16 mL/kg/min. (adjusted for age), stable for at least one month on digoxin, diuretics, and vasodilators (**ACE inhibitors**).

DETD Concurrent **ACE inhibitor** therapy.

DETD **Diabetes** mellitus or impaired glucose tolerance.

AN 97:96744 USPATFULL

TI Gene encoding cardiac hypertrophy factor

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AI US 1995-443952 19950517 (8)

RLI Division of Ser. No. US 1994-286304, filed on 5 Aug 1994, now patented, Pat. No. US 5571893, issued on 5 Nov 1996 which is a continuation-in-part of Ser. No. US 1994-233609, filed on 25 Apr 1994, now patented, Pat. No. US 5534615, issued on 9 Jul 1996

DT Utility

EXNAM Primary Examiner: Arthur, Lisa B.

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CLMN Number of Claims: 18

ECL Exemplary Claim: 1,8,9,10

DRWN 8 Drawing Figure(s); 8 Drawing Page(s)

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated CT-1, isolated DNA encoding CT-1, and recombinant or synthetic methods of preparing CT-1 are disclosed. These CT-1 molecules are shown to influence hypertrophic activity and neurological activity. Accordingly, these compounds or their antagonists may be used for treatment of heart failure, arrhythmic disorders, inotropic disorders, and neurological disorders.